Long-term outcomes in critically ill patients with acute respiratory failure

Mariachiara Ippolito[a,b], *Alberto Nicolò Galvano*[b] *and Andrea Cortegiani*[a,b]

Purpose of review
This review aims to explore the latest evidence on long-term outcomes in patients admitted to the ICU because of acute respiratory failure (ARF).

Recent findings
As the survival rate of critically ill patients with acute respiratory failure improves, long-term mortality and disability still influence the quality of life of survivors and their caregivers. Patients admitted to the ICU because of ARF are at risk of developing the postintensive care syndrome, which presents with physical, cognitive and mental symptoms, all of which may impair their quality of life. Caregivers seem to be affected as well, which may lead to intergenerational trauma. The need for more care, including prone positioning, invasive support (e.g. mechanical ventilation, ECMO) and deep sedation are probably adjunctive risk factors for poor long-term outcomes.

Summary
There is not much data on the long-term outcomes of patients who have survived ARF. More follow-up studies should be conducted, especially in centers providing higher levels of costly care (e.g. ECMO). Randomized controlled trials on interventions for ARF should include patient-centered long-term outcomes in addition to mortality rates. The high mortality rates associated with ARF mandate collaboration among multiple centers to achieve an adequate sample size for studying the long-term outcomes of survivors.

Keywords
acute respiratory failure, cognitive impairment, long-term outcomes, mental dysfunction, physical disability

INTRODUCTION

Acute respiratory failure (ARF) is one of the most frequent indications for ICU admission [1]. ARF is characterized by inadequate gas exchange caused by either an acute pulmonary disorder or an acute systemic disorder, which secondarily affects respiratory function (e.g. sepsis, trauma, burns). Severe ARF leading to ICU admission is associated with high mortality rates despite the improvements in ICU technologies and quality of care over time [2,3]. Over the last decades, there have been advances in extracorporeal support [e.g. extracorporeal membrane oxygenation (ECMO)], imaging, monitoring, and therapeutics (e.g. prone positioning) that have improved overall ICU survival [3,4]. However, the increased survival rate of this cohort of severely affected patients comes with a cost; late mortality and long-term disability have become a major burden for survivors of the most severe presentations of ARF (e.g. severe ARDS). Indeed, patients who are most severely affected in the long-term are usually those who have received the most invasive care, including prone positioning, invasive procedures and support, deep sedation and neuromuscular blockade. And these same ICU patients also commonly have prolonged ICU stays and multiple complications (e.g. nosocomial infections). There is increasing interest in the potential need for prolonged follow-up on survivors of critical illness [5]. Many of these survivors suffer from the postintensive care syndrome (PICS) – a syndrome consisting of impairment in physical, cognitive, or mental health status after critical illness [6]. PICS

[a]Department of Anesthesia, Analgesia, Intensive Care and Emergency. University Hospital Policlinico Paolo Giaccone and [b]Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.). University of Palermo, Palermo, Italy

Correspondence to Professor Andrea Cortegiani, MD, Department of Precision Medicine in Medical, Surgical and Critical Care, University of Palermo, (Me.Pre.C.C.), via del Vespro 129, 90127 Palermo, Italy.
Tel: +39 0916552700; e-mail: andrea.cortegiani@unipa.it

Curr Opin Crit Care 2024, 30:510–522
DOI:10.1097/MCC.0000000000001196

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

SHOUT
SHARE
IT

KEY POINTS

- Long-term outcomes of ARF survivors dramatically affect quality of life of patients and caregivers.
- Latest clinical studies suggest a variable incidence of PICS after severe ARF but apparently without association to days alive without life support or days alive out of hospital.
- More studies should be conducted including nonsurvival-related patient-centered long-term outcomes after ARF.

usually continues well after hospital discharge and imposes on both survivors and their caregivers [7,8].

The aim of this narrative review was to summarize the latest evidence on long-term outcomes in patients admitted to ICU for ARF and to provide a glance to preventive measures and methods to follow-up on these patients.

For the purpose of this review, a systematic search was conducted to seek the most recently published evidence on the topic. The PubMed database was surveyed and relevant studies were selected by the authors and synthesized into the narrative review. The characteristics of included studies are presented in Table 1. Tools commonly used to assess long-term physical, cognitive, mental, quality of life or disability-related outcomes are graphically summarized in Fig. 1.

RISK FACTORS AND PREVENTIVE MEASURES

Many critically ill patients will suffer from the PICS and negative long-term outcomes. Among these critically ill patients, those admitted to the ICU because of ARF and those undergoing mechanical ventilation are most likely to have poor long-term outcomes.

Historically, the Canadian Critical Care Trials group identified a post-acute respiratory distress syndrome (ARDS) syndrome, which includes multidimensional disorders and long-term functional disability associated with persistent muscle wasting and weakness, despite return to normal or near-normal pulmonary function [9].

Several studies have investigated factors associated with the likelihood of suffering from the PICS or a reduced long-term quality of life after surviving ICU admission to hospital discharge.

Bundled care, such as the 'ABCDEF' bundle (A, Assess and manage pain; B, Both awakening and spontaneous breathing trials; C, Choice of sedation; D, Delirium prevention and management; E, Early mobility and exercise; F, Family engagement and empowerment) has proven cost-effective as it increases quality-adjusted life-years after ICU stay [10]. However, implementing such bundles in patients affected by ARF is inherently challenging. Severe ARDS usually presents with a high respiratory drive, which increases the risk of self-inflicted lung injury. This presentation often requires invasive mechanical ventilation. The provision of controlled mechanical ventilation with protective settings (e.g. tidal volume 6 ml/kg of predicted body weight (PBW), Pplat $<$28–30 cmH_2O) usually requires deep sedation (to avoid asynchronous ventilation with breath stacking and possible hypoventilation). Prone positioning may reduce mortality in patients with severe ARDS, but it also increases the risks of physical sequelae (i.e. ICU-acquired weakness, pressure injuries, iatrogenic traumatic injuries) [11]. Similarly, the use of neuromuscular blocking agents or steroids, despite their role in the clinical management of patients with severe ARDS, may accelerate deterioration of muscle function and precipitate ICU-acquired weakness.

The intensity of ICU care was once considered a potential risk factor for poor long-term outcomes. Such a proposition poses an ethical dilemma relating to the appropriateness of providing invasive support in patients with ARF [12]. However, recent evidence seems to contrast with prior beliefs. The long-term outcomes associated with the use of extracorporeal support have recently been described in several small, single-center cohorts [13,14]. One year after hospital discharge, the outcomes of these patients seem no worse than those of other ARDS patients, and they report good health-related quality of life. At least one larger cohort is currently being investigated in a clinical trial in China (NCT03182023). However, a major issue that has arisen with this treatment in ARF is the ethical dilemma of the appropriateness of such intensity of care [15].

Finally, a secondary analysis conducted on more than 2000 critically ill patients enrolled in the COVID STEROID 2 and HOT-ICU trials, showed that days alive without life support or days alive out of hospital were not associated with health-related quality of life [16▪].

PHYSICAL DYSFUNCTION

Physical dysfunction is a pivotal feature of the PICS and is very prevalent among critically ill patients with ARF. These patients have variable clinical presentations of physical dysfunction, including ICU-acquired weakness, critical illness polyneuropathy and myopathy or cachexy [17]. A patient with critical illness-related myopathy presents with flaccid limbs and respiratory weakness, which is unrelated

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1. Characteristics of the studies obtained from the systematic search

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Snyder *et al.*	USA	2023	10.1186/s13054-023-04724-y	Retrospective observational study	110 ARDS survivors, 34 of whom managed with VV-ECMO	1. Pulmonary functions: pulmonary function tests with or without bronchodilator responsiveness, lung volumes, DLCO, and 6MWT 2. Cognitive assessment: Montreal Cognitive Assessment (MoCA) 3. Anxiety/depression: Hospital Anxiety and Depression Scale (HADS) 4. Posttraumatic stress disorder: PTSD Checklist for DSM-5 (PCL-5) Assessed 3 to 6 months after.
Pozzi *et al.*	Italy	2023	10.1097/MAT.0000000000001997	Prospective observational study	34 patients with COVID related ARDS treated with ECMO	1. Nutritional status: BMI and Mini Nutritional Assessment 2. Physical function: according to International Classification of Functioning, Disability and Health 3. Mental and Cognitive assessment: MoCA, HADS-A/HADS-D and Insomnia Severity Index (ISI) 4. Quality of life: SF-36 Assessed at 3, 6 and 12 months.
Martinez *et al.*	Argentina	2023	10.1016/j.hrtlng.2023.06.021	Prospective observational study	40 patients with COVID-related ARDS	Appearance of PICS 30 days after discharge, defined as deterioration in at least one domain: 1. Physical: Barthel Index 2. Cognitive: MoCA 3. Psychological: PHQ-9 and GAD-7
Chow *et al.*	USA	2023	10.1007/s11606-023-08246-9	Qualitative study	24 patients engaged in long-term follow-up from MESSI-COVID trial	Presence of long COVID syndrome assessed with EQ-5D, WHODAS-2 and MRC Dyspnea Scale. Assessed at 1 year
Granholm *et al.*	Denmark, India, Sweden and Switzerland for COVID STEROID 2 Denmark, Switzerland, Finland, the Netherlands, Norway, the United Kingdom and Iceland for HOT-ICU trial	2023	10.1111/aas.14231	Secondary analysis of RCT	1000 adult patients for COVID STEROID 2 trial and 2928 adult patients for HOT-ICU trial	1. Days alive without life support (DAWOLS) 2. Days alive out of hospital (DAOOH) 3. EuroQol visual analogue scale (EQ VAS) values 4. EuroQol 5-dimension, 5-level (EQ-5D-5L) index values 5. All-cause mortality Assessed at 6 and 12 months after discharge.
Piva *et al.*	Italy	2023	10.1016/j.jcrc.2023.154285	Prospective observational study	248 adult COVID ARDS patients compared with 48 classic ARDS patients	1. Muscle weakness: Medical Research Council Sum Score (MRCss) and handgrip dynamometry (HGD) 2. Activity limitation: 6MWT and fatigue severity score (FSS) 3. Performance in ADLs: Barthel index 1. Assessed at 6 and 12 months
Deana *et al.*	Italy	2023	10.3390/jcm12031058	Prospective observational study	343 adults with COVID-related ARDS patients	2. Quality of life after ICU discharge: SF-36 3. PTSD: impact of event scale-revised (IES-R) 4. Assessed at 1 year after ICU discharge.
Scaramuzzo *et al.*	Italy	2022	10.1186/s12890-022-02214-5	Prospective observational study	33 adult COVID patients	5. New onset dyspnea assessed with mMRC 6. Respiratory function assessment with FeNO, spirometry, DLCO, oscillometry and EIT Assessed at 1 year

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Hodgson *et al.*	Australia	2022	10.1164/rccm.202110-2335OC	Prospective observational study	98 adult COVID patients 158 adult non-COVID patients	1. Global health: WHODAS 2.0 12L 2. Health status: EQ-6D-5L 3. Anxiety and depression: HADS 4. PTSD: Impact of events-6 scale 5. Cognitive function: Montreal Cognitive Assessment-BLIND 6. Activities of daily living (IADL) Assessed at 6 months follow-up
Forsberg *et al.*	Sweden	2022	10.1111/aas.14054	Prospective observational study	100 adult COVID patients	Primary outcome: 60 days mortality Secondary outcome: 1. Dyspnea (mMRC) 2. General health status (5 option Likert scale, from very good to very bad) Telephone follow-up at 4 months after discharge.
Jaquet *et al.*	France	2022	10.1097/CCM.0000000000005500	Prospective observational study	41 adult COVID-19–associated acute respiratory distress syndrome survivor	1. Functional outcome: mRS and IADL 2. Muscle strength: MRC 3. Global cognitive status: MOCA 4. Anxiety and depression: HADS and QIDS-SR16 5. Insomnia-related symptoms: ISI 6. Posttraumatic stress disorder: PTSD checklist Assessed between 3 and 6 months post-ICU discharge.
Zangrillo *et al.*	Italy	2022	10.1053/j.jvca.2021.11.032	Prospective observational study	56 survivors of COVID-19 ARDS receiving invasive mechanical ventilation	1. Physical recovery and disability: Glasgow Outcome Scale extended, GOSe 2. Autonomy in walking: Functional Ambulation Classification 3. Dyspnea: Borg Category Ratio 10 scale 4. Nutritional status: MNA-SF 5. Quality of life: EQ-5D-3L 6. Anxiety, depression and PTSD: HADS and PTSD checklist of DSM-V 7. Cognitive status: Italian phone version of MMSE Assessed at 1 year follow-up.
Rilinger *et al.*	Germany	2021	10.1186/s13054-021-03821-0	Prospective observational study	53 adult survivors treated with VV-ECMO for severe ARDS that responded to HRQoL questionnaires	1. 6 and 12 months survival 2. HRQoL assessed with HADS, SF-36 and St. Georges Respiratory Questionnaire (SGRQ) Phone interview occurred at a median of 3.9 years after discharge
Gamberini *et al.*	Italy	2021	10.1016/j.rmed.2021.106665	Prospective observational study	178 adult patients COVID-19 ICU survivors	HRQoL assessed via 15D instrument. Assessed at 3 months and 1 year by telephone interview
Turnbul *et al.*	USA	2022	10.1016/j.chest.2021.07.2177	Secondary analysis of a prospective observational study and a RCT	137 patients from ICAP study, 686 from ALTOS study	1. Perceived health: EQ-5D-VAS 2. Symptoms and self-reported function: EQ-5D-3L and SF-36v2 Assessed at 6 and 12 months follow-up.
Gamberini *et al.*	Italy	2021	10.1007/s11136-021-02865-7	Prospective observational study	278 COVID adult survivors	HRQoL assessed with 15D instrument. 90 days follow-up

1070-5295 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Marsh *et al.*	UK	2021	10.1016/j.rmed.2021.106419	Prospective observational study	24 surviving adult patients treated with VV-ECMO therapy and 23 control patients	Before and after illness self-report questionnaire addressing physical difficulties (energy, slowness); language (word-understanding, following conversation); attention (concentration, distraction); memory (for names, personal events, face recognition, forgetting to do things); and mood (anxiety, irritability, depression). Neuropsychological test battery: 1. Intelligence (IQ): Wechsler Abbreviated Scale of Intelligence, 2nd edition (WASI-II), two scale 2. Anterograde memory: Logical memory test (immediate and delayed) Wechsler Memory Scale (WMS-IV), Rey Osterrieth Complex Figure test (delayed visual memory), Doors and People test (visual and verbal recall and recognition memory) 3. Working memory: Digit Span 4. Executive functions: Hayling sentence completion test (response initiation/suppression), Brixton spatial anticipation test (rule detection) 5. Language and semantic processing: Graded Naming Test (GNT), Pyramids and Palm Trees (PTT) 6. Attention: Test of Everyday Attention (TEA) visual 7. Depression: Beck's Depression Inventory-II (BDI-II) Assessed at 18 months follow-up
Probert *et al.*	USA	2021	10.1016/j.jpsychores.2021.110418	Secondary analysis of RCTs	826 ARDS survivors from ALTOS study	Primary outcome: bodily pain, assessed with SF-36 and Bodily Pain (BP) subscale. Secondary outcome: 1. Anxiety and depression: HADS 2. Functional performance: FPI-SF 3. Cognitive impairment: MMSE Assessed at 6 and 12 months follow-up
Writing Committee for the COMEBAC Study Group *et al.*	France	2021	10.1001/jama.2021.3331	Prospective observational study	478 COVID-19 survivors	1. Respiratory, cognitive, and functional symptoms: Q3PC cognitive screening questionnaire and a checklist of symptoms (phone interview) 2. Quality of life: 36-Item Short-Form Health Survey questionnaire 3. Fatigue: Multidimensional Fatigue Inventory scale 4. Dyspnea: mMRC and 6MWT 5. CT scans 6. Psychological and Cognitive Assessment: Montreal Cognitive Assessment and McNair self-questionnaire 7. Anxiety and depression: HADS, 13-item Beck Depression Inventory score 8. Insomnia: Insomnia severity index 9. PTSD: PTSD checklist, PCL-5 scale Assessed at 4 months follow-up
Su *et al.*	USA	2021	10.1016/j.chest.2021.03.008	Prospective observational study	326 previously employed ARDS survivors	1. Cognitive impairment: MMSE 2. Emotional, interpersonal, physical impairment and pain: Short Form 36 (SF-36) 3. Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue Scale Assessed at 6 and 12 months follow-up using a previously developed employment questionnaire

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
González *et al.*	Spain	2021	10.1016/j.chest.2021.02.062	Prospective observational study	62 adult patients with COVID-19-related ARDS	1. General and respiratory symptoms: mMRC 2. Health-related quality-of-life: SF-12 3. Anxiety and depression: HADS 4. Pulmonary Function Tests: spirometry, lung volume, diffusing capacity 5. Chest CT scan with total severity score Assessed at 3 months follow-up
Monti *et al.*	Italy	2021	10.1111/aas.13812	Prospective observational study	39 adult patients with COVID-19 ARDS	1. Physical recovery and disability: Glasgow Outcome Scale extended, GOSe 2. Autonomy in walking: Functional Ambulation Classification, FAC 3. Self-evaluation of dyspnea: Borg Category Ratio 10, CR-10 4. Nutritional status: Mini Nutritional Assessment – Short Form, MNA-SF 5. Quality of life: Euro Quality 5 Dimensions 3 Levels, EQ5D-3L 6. Psychological outcomes: Hospital Anxiety and Depression Scale, HADS; PTSD Checklist for DSM-5; Insomnia Severity Index, ISI 7. Cognitive status: Italian Telephonic version of the Mini-Mental State Examination, Itel-MMSE Assessed at 2 months follow-up
Apfelbacher *et al.*	Germany	2020	10.1186/s12889-020-08943-8	Prospective observational study	396 adult ARDS survivors	1. Health-related quality of life: Short Form-12 self-report questionnaire (SF-12) 2. Return to work: self report Assessed during follow-up, up to 1 year after discharge
Neufeld *et al.*	USA	2020	10.1016/j.chest.2020.03.059		732 adult ARDS survivors	1. Fatigue measurement: Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) instrument 2. Physical, Cognitive, and Mental Health Measures: Short Form-36 Version 2 (SF-36v2), Functional Performance Inventory-Short Form, Mini-Mental State Examination, 3. Post-Traumatic Distress Syndrome symptoms: Impact of Events Scale-Revised 4. Anxiety and depression: Hospital Anxiety and Depression Scale Assessed at 6 and 12 months follow-up
Grasselli *et al.*	Italy	2019	10.1097/ALN.0000000000002624	Prospective observational study	84 survivors to ARDS, 34 treated with ECMO	1. Pulmonary function tests, 2. Computed tomography of the chest, 3. Health-related quality-of-life questionnaires Assessed at 1 year
Lee *et al.*	USA	2019	10.1097/CCM.0000000000003774	Secondary analysis of RCTs	162 family members of 120 ARDS survivors	1. PTSD symptoms: Post-Traumatic Stress Disorder Checklist – Civilian Version (PCL-C) 2. Depression symptoms: Patient Health Questionnaire (PHQ-9) 3. Anxiety symptoms: Generalized Anxiety Disorder scale (GAD-7) Assessed at 3 months follow-up after discharge on family members

1070-5295 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Sanfilippo *et al.*	Italy	2019	10.23736/S0375-9393.19.13095-7	Prospective observational study	33 ARDS patients treated with VV-ECMO	1. Health-related quality of life (HR-QoL): 36-Item Short-Form Health Survey (SF-36) 2. Psychological measures: Hospital Anxiety and Depression Scale (HADS, for risks of anxiety/depression), Centre for Epidemiologic Studies Depression (CES-D) for risk of depression, Impact of Event Scale revised (IES-R) for symptoms of posttraumatic stress disorder (PTSD) Median follow-up of 2.7 years.
Patel *et al.*	USA	2018	10.1097/CCM.0000000000003124	Prospective observational study	81 Adult patients with ARDS	Functional independence: independence in all ADLs and independent ambulation as reported by the patient. Assessed at 1 year with phone interview
von Bahr *et al.*	Sweden	2018	10.1097/CCM.0000000000002992	Prospective observational study	38 long-term severe respiratory failure survivors treated with ECMO	Cognitive function: Wechsler Adult Intelligence Scale, Rey Auditory Verbal Learning Test; Rey Complex Figure Test, Free and Cued Selective and Reminding test, Delis–Kaplan Executive Function System Median of 9 years follow-up.
Bienvenu *et al.*	USA	2018	10.1007/s00134-017-5009-4	Retrospective observational study	186 Adult ARDS patients. 123 patients completed 5 years follow-up	1. Anxiety and depression symptoms: Hospital Anxiety and Depression Scale (HADS) 2. PTSD symptoms: Impact of Event Scale-Revised (IES-R) Up to 60 months follow-up
Wilson *et al.*	USA	2018	10.1097/CCM.0000000000002927	Prospective observational study	743 patients mechanically ventilated for acute respiratory failure and without functional impairment at baseline	Functional impairment: Barthel index Follow-up 1 year and 5 years after extubation
Galazzi *et al.*	Italy	2018	10.1097/DCC.0000000000000278	Prospective observational study	17 adult patients treated with VV-ECMO for acute respiratory distress syndrome	Quality of Life: EuroQol-5 Dimension questionnaire. Phone interview at least 1 year after hospital discharge
Eakin *et al.*	USA	2017	10.4037/ajcc2017834	Prospective observational study	48 adult patients from ALTOS and ROMA study	Survivor's health, well being, and recovery as well as physical, mental, and social health domains of the PROMIS framework. Assessed 5–18 months after discharge from ICU with semistructured, telephone-based interviews using a written interview guide with open-ended questions
Kamdar *et al.*	USA	2018	10.1136/thoraxjnl-2017-210217	Qualitative study	138 long-term survivors of ARDS	1. Employment data and return to work: self-report survey instrument 2. Survivors' health-related quality of life status 2, 3, 4 and 5 years after ARDS: Medical Outcomes Study Short-Form 36 version 2 (SF-36) Up to 5 years follow-up starting from 2 years survivors.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Brown *et al.*	USA	2017	10.1136/thoraxjnl-2017-210337	Prospective observational study	645 ARDS patients	1. Quality of life: EuroQOL (EQ-5D-3L) 2. Physical and mental health: SF-36v2 Health Survey 3. Fatigue: Functional Assessment of Chronic Illness Therapy (FACIT) 4. Cognitive status: Telephone Mini Mental State Exam (T-MMSE) 5. Anxiety, depression and PTSD: Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale-Revised (IES-R) 6. Physical function: Functional Performance Inventory – Short Form (FPI) Assessed at 6 months
Pfoh *et al.*	UK, USA, Australia	2016	10.1513/AnnalsATS.201510-705OC	Secondary analysis of RCTs	1229 survivors of acute respiratory failure from the five studies	1. HRQoL: SF-36 2. Anxiety and Depression: HADS and DASS 3. PSTD symptoms: Davidson Trauma Scale (DTS), Impact of Event Scale (IES) and IES revised (IES-R) Assessed at 6 and 12 months
Chan *et al.*	USA	2016	10.1097/CCM.0000000000001760		184 ARDS survivors from ALTOS study and 122 from ICAP study with 4-m gait speed assessment	4-m gait speed assessment as measure of physical function in ARDS survivors. Evaluated at 12 months follow-up for ALTOS and 60 months follow-up for ICAP
Pfoh *et al.*	USA	2015	10.1186/s13054-015-0934-5	Secondary analysis of prospective observational studies and RCT	242 survivors of acute respiratory failure from ALTOS and ABC studies	Superior performance of a detailed neuropsychological test battery versus MMSE. Up to 12 months of follow-up
Skinner *et al.*	Australia, New Zealand	2015	10.1513/AnnalsATS.201412-568OC		62 H1N1 influenza survivors who were mechanically ventilated	Comparison of HR-QoL of patients mechanically ventilated H1N1 influenza survivors with general healthy population and ICU survivors. Phone interview administering Short Form-36 version 2 (SF36V2) and Assessment of Quality of Life (AQoL-4D) Assessed at 6 or 12 months after ICU discharge to compare
Li *et al.*	China	2015	PMID: 25556379	Secondary analysis of a RCT and a prospective observational study	9 ARDS survivors	Morphological changes in lung parenchyma assessed with lung HRCT scans. 1, 3, 6, and 12 months after the withdrawal of severe ARDS survivors rescued by ECMO
Needham *et al.*	USA	2014	10.1164/rccm.201401-0158OC		203 acute lung injury survivors	Evaluate risk factors for three measures of physical impairments in survivors of ALI. 1. Overall extremity strength: Manual muscle testing strength 2. Physical functioning: 6MWT 3. HRQoL: SF-36 PF Assessed at 6 and 12 months.

1070-5295 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Needham *et al.*	USA	2013	10.1164/rccm.201304-0651OC	Secondary analysis of RCTs	174 acute lung injury survivors	Physical performance: 1. 12-month 6-min-walk test (6MWT) 2. 4-m timed walk speed (in m/s) 3. Manual muscle testing: Medical Research Council sum score 4. Spirometric test: maximal inspiratory pressure, FVC, FEV1 5. BMI and percentage fat and muscle areas based on upper arm anthropometric assessment Cognitive Impairment: 1. Executive function: Hayling Sentence Completion Test scaled score 2. Language: Controlled Oral Word Association (COWA) total score 3. Immediate and delayed memory: Logical Memory I and Logical Memory II age-adjusted scaled scores 4. Verbal reasoning and concept formation: Similarities age-adjusted scaled score 5. Attention and working memory:Digit Span age-adjusted scaled score Assessed at 6 and 12 months after acute lung injury
Wilcox *et al.*	Canada	2013	10.1378/chest.12-0685		24 survivors of severe ARDS	1. Primary outcome: chest radiologic abnormalities on HRCT scan at 5 years 2. Secondary outcome: relationship between radiologic abnormalities and pulmonary symptoms, pulmonary function test abnormalities, and health-related quality of life [Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)] at 5-year follow-up. Evaluation at 3, 6, 12, and 24 months and then yearly up to 5 years after discharge from the ICU
Hodgson *et al.*	Australia	2012	10.1186/cc11811	Prospective observational study	21 ARDS patients treated with ECMO as a rescue therapy	Survival and long-term quality of life assessment: Short-Form 36 (SF-36) and the EuroQol health-related quality of life questionnaire (EQ5D) Assessed with a median follow-up of 8.4 months and compared with international data from other research groups
Luyt *et al.*	France	2012	10.1378/chest.11-2196	Prospective observational study	37 survivors of A(H1N1)-associated ARDS	1. General health: interview about symptoms and activities after discharge 2. Physical function: physical examination including weight and muscle-strength testing 3. Lung function: standard pulmonary function testing, ABG at rest, chest CT scan 4. Cardiopulmonary function: maximal oxygen consumption 5. HRQoL: 36-Item Short-Form Health Survey (SF-36) 6. Anxiety and depression: Hospital Anxiety and Depression Score 7. Symptoms of posttraumatic stress disorder (PTSD): Impact of Event Scale 1-year outcomes according to use or no use of extracorporeal lung assist (ECLA), using its need as an ARDS severity surrogate

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Table 1 (*Continued*)

First author	Country	Year	DOI/PMID	Design	Population	Long-term outcomes
Mikkelsen *et al.*	USA	2012	10.1164/rccm.201111-2025OC	Prospective observational study	75 ACOS participants that completed follow-up at 12 months	Neuropsychological functions tested with a validated telephone battery of standardized neuropsychological tests. Assessed at 2 and 12 months post-hospital discharge
Adhikari *et al.*	Canada	2011	10.1378/chest.11-1667	Prospective observational study	48 survivors of ARDS	1. Depression: Beck Depression Inventory II [BDI-II] 2. Memory complaints: Memory Assessment Clinics Self-Rating Scale [MAC-S] 3. Return to work 4. Health-related quality of life: SF-36 Assessed at 5 years after ICU discharge.
Herridge *et al.*	Canada	2011	10.1056/NEJMoa1011802	Prospective observational study	109 ARDS survivors	1. General health: detailed interview about symptoms 2. Physical functions: physical examination (including muscle-strength measurements) 3. Pulmonary function: pulmonary-function testing, chest radiography, and the 6-min-walk test with continuous oximetry 4. Health-Related Quality of Life: Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Family caregivers also interviewed. Evaluation at 3, 6, and 12 months and at 2, 3, 4, and 5 years after discharge from the intensive care unit.
Masclans *et al.*	Spain	2011	10.1378/chest.10-2438	Prospective observational study	38 ARDS survivors	1. General health and HRQoL: clinical interrogation and physical examination, Spanish version of the Nottingham Health Profile (NHP) as an HRQL test 2. Pulmonary function testing (PFT): MasterLab system 3. High-resolution chest CT (HRCT) scan study 4. Exercise test: 6-min walk test 6 months after discharge follow-up
Cox *et al.*	USA	2009	10.1097/CCM.0b013e3181b6f64a	Prospective observational study	23 patients and 24 caregivers completed interview	Semi-structured interview about qualitative changes on daily life: 1. Pervasive memories of critical care 2. The day-to-day impact of new disability 3. Critical illness defining the sense of self 4. Relationship strain and change 5. Coping 1–12 months follow-up

1070-5295 Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

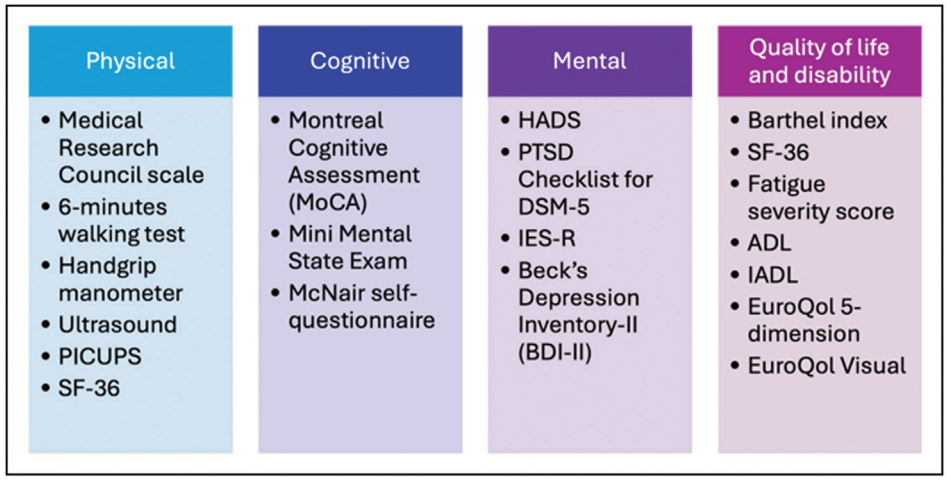

FIGURE 1. Tools used to assess long-term physical, cognitive, mental and quality of life or disability related outcomes.

to a prior condition and had developed during their ICU stay [17]. Polyneuropathy may also present similarly, and differentiating between the two can be challenging if based on physical examination alone. The Medical Research Council (MRC) Scale may be used to assess muscle strength but electrophysiologic tests, ultrasound and muscle biopsy may be required to reach a diagnosis and for periodic assessment [17].

Unresolved physical dysfunction should be formally communicated to the ward team taking over patient treatment at the time of ICU discharge [17]. The hospital discharge note should also include indications for rehabilitation and its goals (e.g. sitting, standing, walking). Both the family and the patient should be informed regarding expected long-term morbidity if expected, including acknowledgment of the higher risk of long-term mortality when compared with patients without residual dysfunction or weakness.

A screening tool, the Post-ICU Presentation Screen (PICUPS), has been recently developed for identifying the needs of ICU survivors in terms of medical and essential care, breathing and nutrition, physical movement and communication, cognition, and behavior [18,19]. This tool has also been validated across 26 acute care hospitals in the United Kingdom.

COGNITIVE AND MENTAL DYSFUNCTION

Both cognitive and mental dysfunction frequently occurs during and after ICU stays for respiratory failure. Cognitive dysfunction is a continuum from acute cognitive dysfunction (e.g. coma, delirium), to long-term cognitive impairment. Cognitive dysfunction may present with features related to a variety of domains – memory, attention, speech competency, and visual–spatial ability [20]. The persistence of such impairments beyond the duration of acute hospitalization may significantly hamper functional recovery as assessed by the Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL) as well as chance to return to work, to maintain social relationships and regaining personal autonomy [20]. Moreover, long-lasting anxiety, depression and posttraumatic stress disorder (PTSD) may impose an additional burden on the cognitive dysfunction associated with critical illness. Indeed, cognitive and mental dysfunctions often co-occur, creating a synergistic negative effect on patients' quality of life after critical illness. Diagnosing the specific type (i.e. psychological and/or cognitive) and intensity of each dysfunction is pivotal for determining which form of support may be most beneficial. However, even acknowledging the existence of such dysfunction may improve quality of life. Caregivers and healthcare providers are often aware of the implications of such dysfunction in terms of symptoms, loss of self, and social impairment.

THE LATEST EVIDENCE

The paucity of ICU studies considering outcomes prioritized by patients after ICU discharge has been repeatedly discussed [21]. The large number of patients admitted with severe ARF due to SARS-CoV-2, many of which had no or only mild comorbidities, has also focused attention on long-term outcomes.

One study conducted of patients admitted to the ICU for severe COVID-19 in Argentina, identified PICS in 64% of survivors at 30 days after discharge. All of the patients with PICS had some physical impairment, 41% had a cognitive impairment and

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

32% had some psychological impairment [22▪]. The multicenter prospective observational Odissea study [23], included 343 COVID-19 patients admitted to nine ICUs (March 2020 to February 2021). One year after ICU discharge, 31.8% of the patients had PTSD as assessed with the Impact of Event Scale-Revised (IES-R), and these patients had significantly lower HRQoL as assessed by the 36-Item Short Form Survey (SF-36) when, compared with those without PTSD.

During the same years, Piva *et al.* conducted a prospective observational study of the physical performance and activities of daily living measured at 6 and 12 months in 248 patients with COVID-19-related ARDS. These authors also compared this cohort with a historical cohort of 48 patients with ARDS due to other causes [24]. The patients were assessed using the Medical Research Council Scale (MRCs), 6-min walk test (6MWT), handgrip dynamometry (HGD), fatigue severity score (FSS) and the Barthel index. The historical control group of survivors of ARDS had an independent increased risk for long-term physical impairment when compared with survivors of COVID-19-related ARDS.

A qualitative study conducted in the United States surveyed a sub-cohort of patients from the MESSI-COVID study who survived severe COVID-19 1 year after the event [25▪]. Survivors claimed that clinicians were often so focused on their physical health, limited attention and care were dedicated to important symptoms related to cognitive and psychological health, such as 'brain fog'. Yet these comprised much of their post-ICU burden of symptoms. However, discrepancies have been described between self-reported impairment and neuropsychological test results, and such findings suggest that this issue may be related not only to physician attention but also to the adequacy of the current assessment tools [26]. Moreover, socioeconomical status disproportionately affected the likelihood of long-COVID. Substantial financial or social support systems were found to be associated with a lower likelihood of long-term effect of COVID-19.

A single-center prospective observational study has been conducted on 25 COVID-19 ECMO patients at 3-month, 6-month, and 12-month follow-up visits after discharge, and investigated physical, cognitive, and psychological outcomes [27]. The study described 67% of patients with muscle weakness and 23% of patients experienced fatigue. Cognitive impairment, anxiety, and depression were stably present in 20–30% of the patients. However, up to 86% were found able to return to work at 1 year.

A multicenter retrospective cohort study including 110 patients with ARDS in 2019, of which 34 treated with ECMO, had found similar functional outcomes in ECMO and non-ECMO patients at a follow-up visit conducted 3–6 months after discharge [28]. The testing included pulmonary function tests, the Montreal Cognitive Assessment, the PTSD Checklist for DSM-5 and the Hospital Anxiety and Depression Scale (HADS). The results were also confirmed by the authors after adjusting for age, SOFA, COVID-19 status, or length of hospitalization, and are in line with previous literature [15].

Although many of the studies published in recent years have focused mainly on COVID-19 patients, which potentially limits the generalizability of their findings, ARF related to COVID-19 ARDS shares important features with ARF due to other causes. Hence the recent evidence produced on the topic of long-term outcomes after ARF has in fact provided greater clarity and homogeneity in definitions and outcomes nonetheless.

LONG-TERM EFFECTS ON CAREGIVERS OF PATIENTS WITH ACUTE RESPIRATORY FAILURE AND ARDS

The impact of ARDS or COVID-19-related ARDS on the long-term outcomes of caregivers has only recently been investigated [29,30]. Azoulay *et al.* found that family members of patients with COVID-19 disease, as compared with other causes of ARDS were more likely to have symptoms of PTSD 90 days after ICU discharge [30].

Overall, such evidence is in line with previous literature, confirming that the impact of negative long-term outcomes of patients who survived critical illness also extends to caregivers. These may manifest as anxiety, depression, posttraumatic stress symptoms, suicidal ideation, increased mortality, and also extend to financial strain. Taken together, these form a broad platform for creating intergenerational trauma [31].

CONCLUSION

The long-term outcomes of survivors of ICU admission because of aARF deserve a greater amount of attention than they have been given thus far. There is a need to follow-up on these patients after hospital discharge especially in centers providing invasive and expensive care. When planning randomized controlled trials related to the treatment of patients with ARF in the ICU patient-centered long-term outcomes must be investigated in addition to survival. Collaboration among centers should be encouraged to reach adequate sample size on long-term outcomes of survivors of such syndromes with high in-hospital mortality rates.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Vincent J-L, Akça S, de Mendonça A, *et al.* The epidemiology of acute respiratory failure in critically ill patients. Chest 2002; 121:1602–1609.
2. Bellani G, Laffey JG, Pham T, *et al.,* LUNG SAFE Investigators, ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016; 315:788–800.
3. Grasselli G, Calfee CS, Camporota L, *et al.,* European Society of Intensive Care Medicine Taskforce on ARDS. ESICM guidelines on acute respiratory distress syndrome: definition, phenotyping and respiratory support strategies. Intensive Care Med 2023; 49:727–759.
4. Matthay MA, Arabi Y, Arroliga AC, *et al.* A new global definition of acute respiratory distress syndrome. Am J Respir Crit Care Med 2024; 209:37–47.
5. Latronico N, Eikermann M, Ely EW, Needham DM. Improving management of ARDS: uniting acute management and long-term recovery. Crit Care 2024; 28:58.
6. Needham DM, Davidson J, Cohen H, *et al.* Improving long-term outcomes after discharge from intensive care unit. Crit Care Med 2012; 40:502–509.
7. Prescott HC, Sjoding MW, Langa KM, *et al.* Late mortality after acute hypoxic respiratory failure. Thorax 2018; 73:618–625.
8. Cameron JI, Chu LM, Matte A, *et al.,* RECOVER Program Investigators (Phase 1: towards RECOVER), Canadian Critical Care Trials Group. One-year outcomes in caregivers of critically ill patients. New Engl J Med 2016; 374:1831–1841.
9. Herridge MS, Cheung AM, Tansey CM, *et al.,* Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. New Engl J Med 2003; 348:683–693.
10. Collinsworth AW, Priest EL, Masica AL. Evaluating the cost-effectiveness of the abcde bundle: impact of bundle adherence on inpatient and 1-year mortality and costs of care∗. Crit Care Med 2020; 48:1752–1759.
11. Guérin C, Reignier J, Richard J-C, *et al.,* PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. New Engl J Med 2013; 368:2159–2168.
12. Combes A, Hajage D, Capellier G, *et al.,* EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. New Engl J Med 2018; 378:1965–1975.
13. Lucchini A, Villa M, Giani M, *et al.,* Irccs San Gerardo Follow-Up Group. Long term outcome in patients treated with veno-venous extracorporeal membrane oxygenation: A prospective observational study. Intensive Crit Care Nurs 2024; 82:103631.
14. Rilinger J, Krötzsch K, Bemtgen X, *et al.* Long-term survival and health-related quality of life in patients with severe acute respiratory distress syndrome and veno-venous extracorporeal membrane oxygenation support. Crit Care 2021; 25:410.
15. Grasselli G, Scaravilli V, Tubiolo D, *et al.* Quality of life and lung function in survivors of extracorporeal membrane oxygenation for acute respiratory distress syndrome. Anesthesiology 2019; 130:572–580.
16. ■ Granholm A, Schjørring OL, Jensen AKG, *et al.* Association between days alive without life support/out of hospital and health-related quality of life. Acta Anaesthesiol Scand 2023; 67:762–771.

This secondary analysis conducted on more than 2000 critically ill patients showed that days alive without life support or days alive out of hospital were not associated with health-related quality of life.

17. Latronico N, Rasulo FA, Eikermann M, Piva S. Critical illness weakness, polyneuropathy and myopathy: diagnosis, treatment, and long-term outcomes. Crit Care 2023; 27:439.
18. Puthucheary Z, Brown C, Corner E, *et al.* The Post-ICU presentation screen (PICUPS) and rehabilitation prescription (RP) for intensive care survivors part II: Clinical engagement and future directions for the national Post-Intensive care Rehabilitation Collaborative. J Intensive Care Soc 2022; 23:264–272.
19. Turner-Stokes L, Corner EJ, Siegert RJ, *et al.* The post-ICU presentation screen (PICUPS) and rehabilitation prescription (RP) for intensive care survivors part I: development and preliminary clinimetric evaluation. J Intensive Care Soc 2022; 23:253–263.
20. Bødker Hanifa AL, Svenningsen H, Møller AN, *et al.* Cognitive impairment in critically ill patients and former critically ill patients: a concept analysis. Aust Crit Care 2024; 37:166–175.
21. Gaudry S, Messika J, Ricard J-D, *et al.* Patient-important outcomes in randomized controlled trials in critically ill patients: a systematic review. Ann Intensive Care 2017; 7:28.
22. ■ Martínez E, Aguilera C, Márquez D, *et al.* Post intensive care syndrome in survivors of COVID-19 who required mechanical ventilation during the third wave of the pandemic: a prospective study. Heart Lung 2023; 62:72–80.

This prospective observational study provides insight on PICS in a middle-income country, highlighting a situation in line with other studies.

23. Deana C, Vetrugno L, Cortegiani A, *et al.* Quality of life in COVID-related ARDS Patients One Year after Intensive Care Discharge (Odissea Study): a multicenter observational study. J Clin Med 2023; 12:1058.
24. Piva S, Pozzi M, Bellani G, *et al.,* LOTO Investigators. Long-term physical impairments in survivors of COVID-19-associated ARDS compared with classic ARDS: a two-center study. J Crit Care 2023; 76:154285.
25. ■ Chow CP, Chesley CF, Ward M, *et al.* Patients' perspectives on life and recovery 1 year after COVID-19 hospitalization. J Gen Intern Med 2023; 38:2374–2382.

This qualitative study, focusing on patients' point of view on their disease and recovery, provides an insight on perceived impact of caring, highlighting important individual experiences (e.g. trust in clinicians as facilitator of recovery).

26. Marsh LC, Leach RM, Blane J, *et al.* Long-term cognitive and psychiatric outcomes of acute respiratory distress syndrome managed with Extracorporeal Membrane Oxygenation. Respir Med 2021; 183:106419.
27. Pozzi M, Giani M, Andreossi M, *et al.,* Monza Follow-Up Study Group. Long-term physical, cognitive, and psychological outcomes in severe COVID-19 patients managed with extracorporeal membrane oxygenation: a prospective study. ASAIO J 2023; 69:e376–e383.
28. Snyder M, Njie BY, Grabenstein I, *et al.* Functional recovery in a cohort of ECMO and non-ECMO acute respiratory distress syndrome survivors. Crit Care 2023; 27:440.
29. Sanfilippo F, Ippolito M, Santonocito C, *et al.* Long-term functional and psychological recovery in a population of acute respiratory distress syndrome patients treated with VV-ECMO and in their caregivers. Minerva Anestesiol 2019; 85:971–980.
30. Azoulay E, Resche-Rigon M, Megarbane B, *et al.* Association of COVID-19 acute respiratory distress syndrome with symptoms of posttraumatic stress disorder in family members after ICU discharge. JAMA 2022; 327:1042–1050.
31. Herridge MS, Azoulay É. Outcomes after critical illness. New Engl J Med 2023; 388:913–924.

Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.